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NATIONAL HEALTH INSURANCE.

MEDICAL RESEARCH COMMITTEE.

MEMORANDUM UPON SURGICAL SHOCK AND SOME ALLIED CONDITIONS.

27th February, 1917.

SURGICAL SHOCK AND SOME ALLIED CONDITIONS.

The phenomenon of oligæmia—or reduction of the volume of the blood in effective circulation—has figured prominently in the theories of surgical and traumatic shock (due, in the main, to American investigators) which have been current during recent years. There is no need to emphazise the importance at the present time of this condition, or that of the acute circulatory failure, similar to this in so many respects, which characterises some of the graver forms of infection and toxæmia. Information has reached the Medical Research Committee concerning some separate experimental enquiries into these conditions which are at present in progress on behalf of the Committee, and which promise to throw light on the production, by causes which have so little immediately obvious connection with one another, of these groups of symptoms having so many points in common.

It appears to the Committee most desirable that clinical observations, bearing on the importance of the different suggested factors in the genesis of shock and allied conditions, should proceed concurrently with the further experimental investigations. They have, therefore, with the consent and aid of the investigators concerned—to whom they are greatly indebted—prepared the following preliminary notes for circulation among those having opportunity for clinical observation, and they have ventured to add some suggestions for the practical application of the results already gained, which seem to them worthy of attention and trial.

I.

H. H. Dale and P. P. Laidlaw, whose primary object was a closer analysis of the shock-like phenomena produced by injection of various protein and bacterial poisons, of the sensitising antigen into an anaphylactic animal, etc., resumed, in the first instance, their examination of the action of the base β. Iminazolylethylamine ("Histamine"), the shock-like action of which they described some years ago. Taking readings of the hæmoglobin value of the arterial blood with Haldane's hæmoglobinometer, or of the percentage volume of corpuscles in the blood with a hæmotocrit, they find that the pro-

found fall of blood-pressure produced by this substance is accompanied by a striking concentration of the blood, amounting in some cases to a loss of one-half the original volume of plasma in about five minutes. The liver appears to be the organ most actively concerned in this reduction of the plasma-volume; but it is not exclusively responsible, for the phenomenon occurs, though less regularly, when the drug is injected after exclusion of all the abdominal viscera. The concentration is apparently effected not merely by loss of water and diffusible constituents, but by the passage into the tissues and lymph-spaces of all the plasma-constituents, since the protein content of the plasma does not rise in proportion to the reduction of volume.

If an animal, moribund from this type of shock, is opened, it is found that the heart is executing muscular beats of moderate vigour, although the arteries are pulseless. The veins are not distended and the great veins fill only very slowly from the periphery if clamped. A large part of the blood, in fact, has disappeared from effective circulation, and the weakness of the heart-beat is due to defective inflow from the veins.

The condition cannot wholly be explained by the loss of plasma-volume above described, for Dale and Laidlaw have several cases on record in which the drug produced a " shock " of some severity, with the general signs of oligæmia as above described, but with no loss of plasma, as measured by concentration of corpuscles, or a loss so small as to be quite inadequate to explain the effect. They further regard a loss of tone of the smaller arteries as insufficient to account for the extreme circulatory depression (the still incomplete evidence points rather to these being *constricted* in these circumstances), and provisionally attribute the shock in the first instance to a widening of the whole capilary area in the viscera and the musculature. The active contractility of the capillaries has been frequently described, and important evidence of its existence in man has just been provided by Cotton, Slade and Lewis (Heart 1917). Dale and Laidlaw suppose that, under the action of the poison, the capilary tone is lost, so that, the blood from the arterioles being diffused and stagnant among the slack capillary channels, the quantity of blood reaching the veins is inadequate for the filling of the heart. The cardiac output falls in consequence to a very low level

An attempt will be made to test by direct experiment this hypothesis of circulatory stagnation as the result of general loss of tone of the capillaries. About the main fact—that there is a depletion of the macroscopic vessels both on the arterial and venous sides —there can be no room for doubt; and it will be obvious how this deficiency of blood-volume, relative to the total capacity of the system, will be aggravated by the direct reduction of the blood-volume, owing to loss of plasma into the tissue spaces which usually accompanies it. The already sluggish circulation will be further impeded by the increase of the viscosity of the blood, mainly due to the increase in the proportion of corpuscles to plasma. This change of viscosity has been directly observed by Trevan *(vide infra)*. The slowness of the capillary circulation, again, through the muscles and other tissues needing a plentiful supply of oxygen, will lead to defective oxidation, with resulting acidity, and so to a further tendency

for passage of water by osmosis from the blood, as suggested by Henderson. Lastly, the fall of arterial pressure, owing to defective filling of the chambers of the heart, and the increased viscosity of the blood, will so reduce the rate of the coronary circulation as eventually to interfere with the nutrition and oxygenation of the heart-muscle itself. It will be seen, therefore, that when once the described condition is established, a series of " vicious circles " is set up.

The determination of the change of plasma-volume from hæmoglobinometer readings may be illustrated by an example. From a cat (under ether) an initial sample of arterial blood gave a hæmoglobinometer reading of 80 p.c. When the profound shock produced by intravenous injection of 10 milligrams of the biphosphate of histamine (about 3 milligrams of the base) had fully developed—*i.e.*, about seven minutes after the injection—a second arterial sample gave a hæmoglobinometer reading of 120 p.c. In order to translate these values into relative volumes of corpuscles and plasma, we must know the initial ratio of these volumes, and assume a constancy of hæmoglobin content in the corpuscles. The hæmotocrit showed that the corpuscles originally occupied one-third, and the plasma two-thirds of the blood-volume, which is a normal ratio for a cat. The rise of the hæmoglobinometer reading from 80 to 120 p.c. must be taken to indicate an increase in the proportional volume of corpuscles in the same ratio. So that the percentage of corpuscles has risen from 33.3 to $33.3 \times \frac{120}{80} = 50$. If the volume of corpuscles has remained constant, this change of proportion indicates a fall of plasma-volume from 66.6 to 50 p.c. In other words, the plasma, which originally occupied twice as great a volume as the corpuscles, now occupies a volume equal to that of the corpuscles, so that one half of the plasma has disappeared from the circulation. A hæmatocrit determination on the second sample actually showed the corpuscles and plasma occupying equal volumes, so that the assumption of a practically constant hæmoglobin content in the corpuscles was justified. The only means, other than the loss of one half of the plasma, by which such a change could be effected, would be a *doubling* of the number of red corpuscles in circulation, and it does not seem credible that this could occur in the course of a few minutes. It should be noted, further, that the arterial blood, on which the readings were made, represents a mixture of all the blood reaching the heart from the different organs. Blood taken from the portal vein, when the shock-like condition has been produced, shows an even greater concentration than that from the arteries; and even this portal blood contains an undue proportion of blood from those of the capillaries in the splanchnic area in which the circulation is still relatively effective. It must be supposed, that in many the vanishing arterial pressure is no longer able to maintain a circulation, so that the blood in them is stationary and its concentration extreme.

Being impressed with the similarity of such a condition to surgical " shock," Dale and Laidlaw have made a short series of attempts to produce such a shock in anæsthetised cats, by prolonged manipulation of the abdominal viscera, which, as Mann and others have pointed out, is the only method by which a traumatic shock can be produced in *Carnivora*. In two cases profound shock, with no tendency to spontaneous recovery, was obtained, and in both these

such a rise of hæmoglobin value was observed, concurrently with the onset of the shock, as to indicate a serious depletion of the plasma-volume. In others a less profound shock was obtained, with a tendency to spontaneous recovery when the abdominal wound was closed and the animal left to itself under the anæsthetic; in these no significant change in the hæmoglobin value was observed. In these cases, also, the manipulated bowels became conspicuously reddened and ultimately blueish in appearance, but the blood-pressure could be temporarily driven almost to its original high level by compressing the whole mass of intestinal coils and so driving the blood out of their capillaries into the general circulation. In these cases, therefore, such shock as was obtained seemed to be due purely to stasis in the abdominal capillaries, as previously described by Mann.

Meanwhile, Captain Marshall, R.A.M.C., had commenced a series of observations in France on the hæmoglobin content of the blood in the different classes of case met with in a Casualty Clearing Station. The Committee understand that among Captain Marshall's observations are some on shock, which support the view that loss of plasma into the tissues is an important factor in the condition.

II.

β. Iminazolylethylamine (Histamine) was chosen by Dale and Laidlaw for this investigation as a pure substance, producing effects of the kind under investigation in exact dosage. Effects of the same general type are produced by many products of protein digestion, bacterial products, etc. Among such effects, those due to the so-called toxæmia of gas-gangrene is of special importance at present. The resemblance between the symptoms of this condition and those of surgical shock, or of a severe hæmorrhage, has frequently been described.

An investigation is now being carried out by H. H. Dale and J. McIntosh into the symptoms presented by animals dying after a local infection of the limb-muscles by organisms of the gas-gangrene group, isolated from material obtained from fatal human cases. The onset of a fatal shock-like condition in such experiments has again been found to be associated with a progressive rise in the corpuscular content of the blood pointing to a steady loss of plasma. It may be pointed out that such an effect was perhaps to be expected. The capillaries in the tissues surrounding the infected muscle are so affected that an enormous local outpouring of plasma occurs. Whether the general symptoms are due to passage of the infecting organisms into the general circulation, or to the absorption through the lymph channels of toxic products of the local breakdown of muscle, effects on the general vascular endothelium of a similar kind, though much less in degree than those produced by the concentrated local action, might be expected. A general loss of capillary tone and a morbid increase of permeability of capillary walls might therefore be expected to result from absorption into the general circulation of the fluids from the infected area. The evidence as yet available confirms this expectation, and suggests that there is a fundamental similarity of origin, underlying the similarity of symptoms, between the toxæmia of gas-gangrene and other shock-

like conditions. It must be remembered, however, that failure of the heart from any cause will be attended by some degree of blood-concentration, if the process is sufficiently gradual. More work is needed before the significance of the phenomenon in these cases can be estimated with confidence.

III.

Concurrently with the foregoing investigations, F. A. Bainbridge and J. W. Trevan have been conducting an investigation into the genesis of shock by other means, and the same factor of concentration of the blood has presented itself in their observations. Their experiments hitherto have been mainly concerned with the effects on the portal and systematic venous pressures, and on the general distribution or blood in the circulation, produced by repeated injections or by long-continued, slow infusion of adrenaline. The enquiry was suggested by the fact, demonstrated by Elliott, Cannon and others, that extreme emotion or severe pain, which are factors in some cases of shock, are accompanied by an outpouring of adrenaline from the suprarenal glands. Bainbridge and Trevan have injected adrenaline slowly into a systemic vein in anæsthetised dogs for 20 minutes or longer, at a rate sufficient to maintain the arterial pressure at a supranormal level comparable with that attained during moderate stimulation of a sensory nerve. During the injection the portal pressure rose to and remained at a high level, while the systemic venous pressure was not significantly altered, or even fell slightly. Meanwhile readings with the hæmoglobinometer and the hæmotocrit showed a steady decrease in the volume of the blood-plasma relatively to that of the corpuscles. In one case the hæmoglobin-value rose from an initial 95 p.c. to 129 p.c. Such a relative increase of corpuscular content would involve a large increase in the viscosity of the whole blood; an actual determination showed an increase of viscosity in the proportion of 6.8 to 9.1.

When the injection of adrenaline was stopped, the arterial pressure rapidly fell to a low level while the portal pressure remained high, and the animal passed into a condition of shock, with feeble pulse and shallow respiration. The relation of the portal and systemic venous pressures indicated an obstruction of some kind to the flow of blood through the liver. This was made further evident, in the later stages of the effect, by the sriking turgidity of the liver itself. If the flow of lymph from the thoracic duct was recorded, it was observed to undergo a striking acceleration, as the obstruction in the liver developed in consequence of the infusion of adrenaline. The nature of this obstruction is not yet clear, and will be the subject of further investigation. Its effect, especially after the cessation of the inflow of adrenaline has allowed a dilatation of the splanchnic arterioles, is a collection of a large part of the blood in the congested splanchnic area. When to this is added the steady loss of fluid from the blood by exudation into the tissues, it will be seen that the final result, as regards the activity of the heart and the general circulation, will be closely similar to that described above in connection with Dale and Laidlaw's experiments. The failure of the output of

the heart from defective venous inflow, due to reduction of the volume of blood in effective circulation, leads to a profound collapse of the arterial pressure; the loss of plasma into the tissues not only aggravates this defect of volume, but, by increasing the viscosity of the blood, further retards such flow through the capillaries as the low arterial pressure could otherwise maintain; and this retardation yet further checks the venous inflow to the heart. The blood travels very slowly round the body under such conditions, and the supply of oxygen to all the tissues becomes inadequate. This inadequacy is accentuated by defective oxygenation of the arterial blood, which remains dusky in colour even with artificial respiration.

IV.

Some Practical Suggestions and Enquiries.

(A.) The point of most novel interest emerging from the above notes is the importance which the different sets of workers attribute to loss of plasma into the tissue spaces, as a factor in the production of the circulatory failure. The presence of such a factor was suggested by Henderson, Mann and others, but its extent and significance have hitherto been rather vaguely indicated. Such loss of fluid from the blood, causing both deficient volume and excessive viscosity, has for some time been clinically recognised as an essential factor in the collapse occurring in conditions like those of cholera and bacillary dysentery, in which the fluid is lost through more obvious channels.

It is here suggested that clinical observation on changes in plasma-volume in traumatic shock, post-operative shock, and the toxæmia of gas-gangrene may yield valuable information. The only instruments clinically applicable to the detection of such changes are the hæmoglobinometer and the hæmatocrit. It will be evident that the interpretation of such observations will be a more complicated matter than that of results obtained under the controlled conditions of experiment; for an estimate of the plasma volume by these methods depends on the assumption that the volume and hæmoglobin-content of the red corpuscles remains constant. It cannot, for example, be expected that a loss of plasma occurring in shock consequent on an extensive wound, with much hæmorrhage, will be accompanied by an absolutely high hæmoglobin-value or hæmotocrit reading. Again, in a protracted case of toxæmia from gas-gangrene, the observation will be vitiated by the probability that, though plasma may be draining from the vessels into the tissue spaces, a coincident destruction of red corpuscles is taking place. It is hoped, however, that a careful selection of suitable cases for observation, and attention rather to change of the corpuscular content, as shown in a series of observations at short intervals, than to the absolute initial value, will enable information to be obtained as to the significance of this factor. It may be suggested that cases of traumatic shock without serious hæmorrhage, of post-operative shock, of intestinal obstruction, of extensive burning, of anaphylactic shock, and of the rapid, fulminating type of toxæmia from gas gangrene, are likely to give relatively uncomplicated data for this purpose.

(B.) The experimental results suggest that the removal of blood from effective circulation may be brought about in more than one

way. It would be of interest to know whether different types of shock can be clinically recognised; in particular, whether a type with circulatory obstruction in the liver, as shown by swelling of this organ and congestion of the portal vein and its tributaries, can be differentiated from a type without this feature; and, if so, whether the nature of the primary cause of the shock has any relation to the type produced.

(c.) *Prevention.*—If shock is, indeed, due to oligæmia, its many points of similarity to the collapse produced by a dangerous hæmorrhage need no explanation. It will further be obvious that an antecedent hæmorrhage, insufficient in itself to produce collapse, may be an important factor in the subsequent onset of shock, in so far as this condition is due to defective volume, apart from increased viscosity of the blood. The normal reaction to a simple hæmorrhage, of sufficient severity to diminish the output of the heart and lower the blood pressure, consists in the abstraction of fluid from the tissues until the volume of the blood is again adequate to maintain the cardiac output. Dale and Laidlaw find that a similar dilution of the blood normally accompanies, and tends to correct, a fall of pressure due to arterial dilatation. In shock, according to the indications of the experiments already described, this restorative reaction fails completely, and fluid continues to pass from the blood, though the arterial pressure has fallen to a very low level. It will be evident, therefore, that, when shock is already imminent, a relatively small hæmorrhage may have a serious influence in determining its onset. Any other causes tending to diminish the blood volume, such as fatigue, exposure, or prolongued astinence from food and water, may be expected to predispose to shock for a like reason. Mention should be made also of the possibility that measures preparatory to an operation in hospital, if they include free saline purgation and severe abstinence from food and water, may contribute to the danger. Cases for urgent operation must constantly present themselves to the military surgeon, in which the antecedent conditions are those mentioned above as tending to depletion of the blood-volume, and therefore predisposing to shock. A free supply of fluid, by infusion of physiological saline into the rectum or the subcutaneous tissues, as already used by many surgeons, may be expected to have a special preventive value in such cases. The indications, however, are that such measures, to have any value, must be begun before or early in the operation. When once the condition of shock has been developed, physiological saline, or Ringer's solution, even if injected intravenously in large volume, appears to have a very limited and temporary value ; for the diluted plasma passes with increased rapidity through the slack and permeable walls of the capillaries, and the fluid leaves the circulation almost as quickly as it is run in.

(d.) *Treatment.* Unfortunately, little can be said as yet as to the treatment of shock and allied conditions when once developed. Suggestions only can be made of measures which may be tested with possible advantage and without danger. It is hoped that further experiment may warrant more positive recommendations at a later stage. Pituitary extract causes a prolonged and general contraction of the arterioles, and thereby diminishes the total capacity of the

circulatory system and mitigates the effect of deficient blood-volume. The tendency of adrenaline to produce obstruction to the circulation through the liver, as described above, makes it probable that the use of this substance would, in some cases, eventually aggravate the condition which it was designed to cure ; its action is, in any case, so fugitive as to be of little value. The action of pituitary extract is free from both these drawbacks; its value in some cases is already well recognised, and, with the ordinary measures for restoring and conserving the body-temperature, needs no further mention.

The failure of injections of physiological saline in fully-developed shock has already been mentioned. Experiments already made seem to indicate that better results might be obtained by the use of intravenous injections of hypertonic saline, the value of which in the treatment of cholera and bacillary dysentery is already familiar. Whether the action of these is entirely due to the passage of water into the vessels by osmosis, or in part to a restorative effect of the hypertonic solution on capillary tone, is not clear. In this connection it may be recalled that calcium ions have been found to have a specific action in reducing abnormal permeability of capillaries (*cf.* Wright ; also several papers from the Vienna school). It seems reasonable, therefore, to suggest that a fluid representing a concentrated Ringer solution should be used, rather than one in which only the proportion of sodium chloride is increased. The following formula might be tried :—

Sodium Chloride	2 grammes.
Potassium Chloride	0.05 ,,
Calcium Chloride	0.05 ,,
Water	100 c.c.

and the value of increasing the relative calcium content beyond this proportion might cautiously be tested.

The deficient oxidation occurring in any condition of circulatory failure will lead to an abnormal acidity of the tissues, and thereby tend to raise the concentration and viscosity of the blood in the capillaries. Administration of alkalies should, therefore help to relieve the condition, and injections of sodium bicarbonate, as recommended by Wright for the treatment of gas-gangrene, should form a valuable addition to large injections of a hypertonic saline mixture. The limited solubility of calcium bicarbonate makes it advisable to give the bicarbonate solution as a separate injection. Hogan and Fischer recommend the following formula for an alkaline hypertonic saline :—

Sodium Chloride	28 grammes.
Sodium Carbonate (crystalline) ...	20 ,,
Distilled water	2 litres.

Bayliss recently drew attention to the importance of the factor of viscosity in solutions used to replace blood lost by hæmorrhage. He considered that gum acacia was a suitable substance to add to saline for such purposes, as imparting the requisite viscosity and as being a colloid with a definite osmostic pressure. Hogan and Fischer, on different theoretical grounds, have recommended the addition of 2 per cent. of gelatine to a saline solution for intravenous infusion. It will be evident, from what has been said above, that the aim in

treating shock should be to restore the volume of blood in effective circulation, and at the same time to reduce the abnormal viscosity. While, therefore a small addition of gum to the saline fluid used for injection may be valuable, the proportion of 7 per cent., suggested by Bayliss, as bringing the viscosity of the saline up to that of normal blood, would be unduly high. An addition of 2 or 3 per cent. of gum acacia to the saline solution above suggested might be tried ; but it will be possible to make more definite recommendations when there has been time for experiment with solutions of different formulæ.

The defective oxygenation of even the arterial blood, in experimental shock as above described, suggests that inhalations of oxygen may have some value in these conditions.

The Medical Research Committee will receive gratefully any reports upon clinical studies or experimental observations which may be sent to them as bearing upon the questions raised in this Memorandum. They hope it may be possible later to issue a further Memorandum, or series of Reports, in which further results of the enquiries now in progress may be given, together with such relevant clinical observations as may then be available.

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(127) Wt P5226/162 200 3/17 Wm. C. Ld.